

Award Number:
W81XWH-09-2-0110

TITLE:
Development of a Balance Prosthesis Based on Infrared Nerve
Stimulation

PRINCIPAL INVESTIGATOR:
Daniel J. Lee, M.D.

CONTRACTING ORGANIZATION:
Massachusetts Eye and Ear Infirmary
Boston, MA 02114

REPORT DATE:
November 2010

TYPE OF REPORT:
Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE 30-11-2010		2. REPORT TYPE Final		3. DATES COVERED 01-09-2009 - 31-10-2010	
4. TITLE AND SUBTITLE Development of a Balance Prosthesis Based on Infrared Nerve Stimulation				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-09-2-0110	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Daniel J. Lee MD (Principal Investigator) Email: daniel_lee@meei.harvard.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Massachusetts Eye and Ear Infirmary - Boston, MA 02114				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Military personnel are exposed to hostile combat environments that cause injury to the vestibular system. The resulting deficits can drastically affect productivity, independence and quality of life. Currently, researchers are developing a range of treatment strategies for these deficits. Electrical stimulation using a vestibular implant has been proposed as a treatment option for patients who sustain significant peripheral vestibular injury that results in chronic imbalance (1-7). While the vestibular implant has the potential to restore some functional capabilities, the effectiveness of electrical stimulation is limited by nonselective activation of surrounding nerves ('crosstalk' or current spread). A recent paradigm shift in neural stimulation is being developed by Aculight and collaborating researchers based on the use of pulsed infrared light (8-15). Infrared nerve stimulation (INS) has the potential to revolutionize the field of sensory replacement neuroprostheses. When applied to the vestibular system, INS or INS-electrical hybrid prostheses will substantially reduce the channel crosstalk compared to conventional electrical prostheses. In addition, they can be made minimally invasive with the use of tiny optical fibers. Development of INS-based vestibular prosthesis technology will improve the quality of life of military personnel suffering from chronic vestibular dysfunction manifested as severe dizziness, ataxia, or chronic vertigo. Our primary objective is to conduct fundamental research that will lay the foundation for development of an effective implantable vestibular prosthesis based on an infrared nerve stimulation and balance sensor technology.					
15. SUBJECT TERMS None provided.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	9	19b. TELEPHONE NUMBER (include area code)

Introduction:

Military personnel are exposed to hostile combat environments that cause injury to the vestibular system. The resulting deficits including severe dizziness, ataxia, or chronic vertigo can drastically affect productivity, independence, and quality of life. Currently, researchers are developing a range of treatment strategies for these deficits. Although rigorous vestibular physical therapy is useful for the rehabilitation of many of these patients with mild to moderate signs and symptoms, few options exist for more severe cases. Electrical stimulation using a vestibular implant has been proposed as a treatment option for patients who sustain significant peripheral vestibular injury that results in chronic imbalance [1-7]. While the vestibular implant has the potential to restore some functional capabilities, the effectiveness of electrical stimulation is limited by nonselective activation of surrounding nerves referred to as crosstalk or current spread. A recent paradigm shift in neural stimulation is being developed by Lockheed-Martin Aculight and collaborating researchers based on the use of pulsed infrared light [8-15]. Infrared nerve stimulation (INS) has the potential to revolutionize the field of sensory replacement neuroprostheses. When applied to the vestibular system, INS or INS-electrical hybrid prostheses will substantially reduce the channel crosstalk compared to conventional electrical prostheses. In addition, they can be made minimally invasive with the use of tiny optical fibers. Development of INS-based vestibular prosthesis technology will improve the quality of life of military personnel suffering from chronic vestibular dysfunction. Funding this research will rapidly accelerate two key emerging technologies that can be combined to create a highly functional neuroprosthesis for restoration of balance in a large population of military war fighters and veterans.

Our primary objective in this proposed work is to conduct fundamental research that will lay the foundation for development of an effective implantable vestibular prosthesis based on infrared nerve stimulation and balance sensor technology.

During this one-year work we proposed to:

- AIM 1. Develop and test a minimally invasive surgical approach for infrared light stimulation of the vestibular periphery in a guinea pig model.
- AIM 2. Determine the threshold of infrared light activation to generate an optically-evoked vestibulo-ocular reflex (oVOR) and/or optical vestibular evoked potential (oVsEP) at the optimal site identified from AIM 1.
- AIM 3. Examine post-experiment histology of vestibular end organs and afferent nerve fibers stimulated with INS from AIM 2.

Body:

The tasks for the current research as outlined in the statement of work are as follows:

Task 1. Develop and test a minimally invasive surgical approach for infrared light stimulation of the vestibular periphery in a guinea pig model (Months 1-4).

- a. Hardware for the proposed experiments will be built by Lockheed Martin Aculight and delivered to MEEI for testing (Month 1-2).
- b. Obtain all necessary institutional approval for working with animals (Month 1-2).
- c. Develop and test a minimally invasive surgical approach to the peripheral vestibular system of the guinea pig using infrared neural stimulation (Months 2-4). Anesthetized guinea pigs will undergo a minimally invasive surgical approach to the inner ear, wherein the lateral semicircular canal will be cannulated with a 200 μ m optical fiber. Infrared stimulation through this optical fiber will be performed to elicit an optically evoked vestibulo-ocular reflex and/or vestibular evoked potential.

Task 2. Determine the threshold of infrared light activation to generate an optically evoked vestibulo-ocular reflex response and/or optical vestibular evoked potential (Months 5-11).

- a. Determine optimal infrared neural stimulation parameters to generate a robust and reliable optically evoked vestibulo-ocular reflex and/or optical vestibular evoked potential (Months 5-8). Conditions of infrared neural stimulation, such as pulse duration and frequency, will be systematically adjusted to maximize responses resulting in the determination of optimal infrared neural stimulation parameters.
- b. Determine threshold infrared neural stimulation parameters to generate a robust and reliable optically evoked vestibulo-ocular reflex and/or optical vestibular evoked potential (Months 8-10). Utilizing the optimal infrared neural stimulation parameters identified in *Task 2a*, the infrared neural stimulation power will be lowered to determine threshold for optically evoked vestibulo-ocular reflexes and/or vestibular evoked potentials.
- c. Comparison of infrared neural stimulation and electrical stimulation (Months 9-11). Electrical stimulation of the peripheral vestibular system will be accomplished via the surgical approach developed in *Task 1c*. Amplitude of nystagmus and vestibular evoked potential parameters including latency, amplitude, and waveform morphology will be compared in electrical stimulation with infrared neural stimulation.

Task 3. Perform histological examination of temporal bones from guinea pigs exposed to infrared neural stimulation (Months 6-12).

Task 4. Prepare results for publication in a peer-reviewed journal (Months 11-12).

The results of the study will be compiled and prepared for publication in a peer-reviewed journal such as the Journal of the Association for Research in Otolaryngology (JARO).

Each of the tasks was managed as follows:

Task 1a required Lockheed Martin Aculight to present MEEI with hardware for the proposed experiments. Lockheed Martin Aculight's optical stimulation device is now in use at MEEI for the proposed optical experiments. The optical device permits the delivery of optical energy (wavelength range 1.849 – 1.865 μ m) to target tissues via a connected optical fiber.

Task 1b required all institutional approval to be obtained for working with animals prior to the initiation of experiments. Intramural (MEEI IRB IACUC) and extramural (USAMRMC ACURO) animal care committee approvals were obtained August 24, 2009 and October 15, 2009, respectively, prior to the initiation of any animal experimental protocols.

Task 1c outlined the development of a minimally invasive surgical approach to the guinea pig peripheral vestibular system using infrared neural stimulation. This approach was developed during the first quarter of research and further refined during the second quarter of work. Minimally invasive approaches for performing a labyrinthotomy have been successfully applied to the lateral and superior semicircular canals for the introduction of both a 200 and 400 micrometer optical fiber into the peripheral vestibular system. Using techniques well known to our lab, electrical stimulation through the minimally invasive labyrinthotomy used for infrared neural stimulation results in a robust and reliable electrically evoked vestibulo-ocular reflex confirming the correct anatomic location of stimulation.

Infrared neural stimulation has been performed by our group through the approaches developed. The initial phases of experimentation were designed to establish a proof-of-concept of infrared neural stimulation within the vestibular system. Despite our efforts optically evoked vestibulo-ocular reflexes were not able to be generated. This finding may represent one of several possibilities, but the two most likely hypotheses based upon our experiments are: Infrared neural stimulation selectively activates small groups of neurons which, if stimulated, may be subthreshold for inducing the vestibulo-ocular reflex and the intrinsic properties of peripheral vestibular neurons do not permit activation by infrared neural stimulation. An alternative method of determining the feasibility of infrared neural stimulation of the peripheral vestibular system was designed in the initial experimental protocol through the measurement of evoked potentials. We were indeed able to generate evoked potentials after the introduction of infrared neural stimulation through a minimally invasive labyrinthotomy. Unexpectedly, the measured responses had the characteristics of auditory rather than vestibular evoked potentials. We have been able to eliminate the evoked response with the addition of broad-band masking noise supporting the concept that the responses are auditory in nature.

Task 2(a-c) was contingent upon the generation of a vestibulo-ocular reflex and/or evoked potential utilizing our minimally invasive surgical approach designed in Task 1c. As outlined above, despite our best efforts, we were not able to generate an optically evoked vestibulo-ocular reflex or a vestibular evoked potential. We were thus unable to determine optimal infrared neural stimulation parameters to generate a robust and reliable optically evoked vestibulo-ocular reflex and/or optical vestibular evoked potential (Task 2a), determine threshold infrared neural stimulation parameters to generate a robust and reliable optically evoked vestibulo-ocular reflex and/or optical vestibular evoked potential (Task 2b), or compare infrared neural stimulation and electrical stimulation (Task 2c).

However, during these experiments we were able to further pursue the interesting finding of generating auditory evoked potentials when infrared neural stimulation was applied through a minimally invasive labyrinthotomy. First, we repeated our approach and confirmed that the potentials generated were consistent with auditory evoked potentials; this was indeed the case. Second, we reasoned that auditory evoked potentials to infrared neural stimulation is a time-dependant phenomenon (that is, a brief stimulus is required to generate a well defined waveform) in the absence of competing sound, that if we applied a broad band masking tone, that the response would be eradicated. When we did apply broad band noise, the evoked potential was abolished. When the masking tone was eliminated, the evoked potential would again return. This represents solid

evidence that the evoked potentials we were measuring were auditory in nature. Third, we were interested about the potential mechanism of action of how infrared neural stimulation, when the probe was placed within the lateral semicircular canal, would generate auditory evoked potentials. We considered two hypotheses. It is possible that the transient heat generated by infrared neural stimulation pulses would generate a pulsed wave that could travel across the vestibule into the cochlea. Alternatively, it is possible that the laser light traveled through the otic capsule and stimulated the cochlea and/or cochlear nerve. To investigate the first hypothesis, we directed the optical fiber in the opposite direction (toward the non-ampullated end of the lateral semicircular canal and away from the cochlea and cochlear nerve, but still within the labyrinthine fluids) and noted that the auditory evoked potentials were no longer present. This evidence refutes the first hypothesis. Also refuting this hypothesis is the fact that we did not see any vestibular evoked potentials or any eye movements with infrared neural stimulation. If infrared neural stimulation worked through the generation of a pressure wave, it would likely deflect the cupula of the canal under stimulation and should result in a detectable response. We believe the infrared neural stimulation is therefore acting upon either the cochlea or cochlear nerve to generate the measured evoked potentials.

Task 3 required histological processing of the temporal bones to ensure that infrared neural stimulation is safe. We are currently in the time-consuming process of decalcifying and staining the temporal bones that were acquired at the end of each individual experiment. We will carefully examine these slides once they are ready to complete this task.

Task 4 involves preparing our results for publication in a peer-reviewed journal. We are in the process of reviewing and compiling our physiologic data for submission to a scholarly journal. Prior to submission, we will await the results from Task 3 to incorporate that information into the manuscript. Following this addition, we will be submitting our work on transvestibular auditory stimulation with infrared neural stimulation.

Key Research Accomplishments:

1. We developed a minimally invasive approach to the guinea pig peripheral vestibular system and successfully placed optical fibers to carry infrared neural stimulation.
2. We discovered striking and exciting findings that infrared neural stimulation through a minimally invasive labyrinthotomy results in the generation of auditory evoked potentials.
3. We investigated several hypothetical mechanisms through which infrared neural stimulation through a minimally invasive labyrinthotomy results in the generation of auditory evoked potentials. We believe, as a result of these experiments, that direct stimulation of the cochlea and/or cochlear nerve is the most likely mechanism of action.

Reportable Outcomes:

As the histologic analyses of the experimental tissue are not yet complete due to the time required to allow for tissue processing (a time-consuming technique due to the need for decalcification of the bony inner ear), we plan to submit an abstract for the 2012 ARO Midwinter Meeting in San Diego, California, and a manuscript to be submitted to *Otology and Neurotology* is under preparation.

Conclusions:

Infrared neural stimulation of the peripheral vestibular system does not result in the generation of an observable vestibulo-ocular reflex or vestibular evoked potential. We hypothesize that either optical stimulation recruits fewer neurons in the peripheral vestibular system than is required to generate these responses, or nerves of the peripheral vestibular system are not as responsive to INS as those neurons in the auditory periphery. However, transvestibular infrared neural stimulation does generate a reliable and robust auditory evoked potential. It is likely that this occurs through direct stimulation of the cochlear nerve or cochlea. Our findings may provide the foundation for future minimally invasive auditory implants based on infrared neural stimulation that would preserve residual hearing in the partially deafened cochlea.

References:

1. Gong, W. and D.M. Merfeld, *Prototype neural semicircular canal prosthesis using patterned electrical stimulation*. *Ann Biomed Eng*, 2000. **28**(5): p. 572-81.
2. Gong, W. and D.M. Merfeld, *System design and performance of a unilateral horizontal semicircular canal prosthesis*. *IEEE Trans Biomed Eng*, 2002. **49**(2): p. 175-81.
3. Lewis, R.F., et al., *Vestibular adaptation studied with a prosthetic semicircular canal*. *J Vestib Res*, 2002. **12**(2-3): p. 87-94.
4. Lewis, R.F., et al., *Vestibular influences on tilt perception and postural control in rhesus monkey*. *Neuroscience Abstracts* 2007, 2007.
5. Lewis, R.F., C. Haburcakova, and D.M. Merfeld, *Tilt psychophysics measured in nonhuman primates*. *Ann N Y Acad Sci*, 2005. **1039**: p. 294-305.
6. Merfeld, D.M., et al., *Acclimation to chronic constant-rate peripheral stimulation provided by a vestibular prosthesis*. *IEEE Trans Biomed Eng*, 2006. **53**(11): p. 2362-72.
7. Merfeld, D.M., et al., *Chronic vestibulo-ocular reflexes evoked by a vestibular prosthesis*. *IEEE Trans Biomed Eng*, 2007. **54**(6 Pt 1): p. 1005-15.
8. Izzo, A.D., et al., *Laser stimulation of the auditory nerve*. *Lasers Surg Med*, 2006. **38**(8): p. 745-53.
9. Izzo, A.D., et al., *Selectivity of neural stimulation in the auditory system: a comparison of optic and electric stimuli*. *Journal of Biomedical Optics*, 2007. **12**(2): p. 1-7.
10. Izzo, A.D., et al., *Optical parameter variability in laser nerve stimulation: a study of pulse duration, repetition rate, and wavelength*. *IEEE Trans Biomed Eng*, 2007. **54**(6 Pt 1): p. 1108-14.
11. Richter, C.-P., et al., *Acute and long term deafening effects on optical stimulation of auditory neurons*. *Hear Res*, 2007. **(in review)**.
12. Wells, J.D., Kao, C., Mariappan, K., Albea, J., Jansen, E.D., Konrad, P., Mahadevan-Jansen, A., *Optical Stimulation of Neural Tissue in vivo*. *Optics Letters*, 2005. **30**(5): p. 504-507.
13. Wells, J.D., Kao, C., Jansen, E.D., Konrad, P., Mahadevan-Jansen, A., *Application of Infrared Light for in vivo Neural Stimulation*. *Journal of Biomedical Optics*, 2005. **10**: p. 064003.
14. Wells, J.D., Konrad, P., Kao, C., Jansen, E.D., Mahadevan-Jansen, A., *Pulsed laser versus electrical energy for peripheral nerve stimulation*. *Journal of Neuroscience Methods*, 2006. **163**(2): p. 326-37.

15. Wells, J.D., Kao, C., Jansen, E.D., Konrad, P., Mahadevan-Jansen, *Optically mediated nerve stimulation: Identification of injury thresholds*. Lasers in Surgery and Medicine, 2007. **39**(6): p. 513-26.